

Effects of national adoption of Treat-All guidelines on pre-ART CD4 testing and viral load monitoring after ART initiation: A regression discontinuity analysis

Ellen Brazier, Institute for Implementation Science in Population Health (ISPH), Graduate School of Public Health and Health Policy, City University of New York, New York, NY, USA

Olga Tymejczyk, Institute for Implementation Science in Population Health (ISPH), Graduate School of Public Health and Health Policy, City University of New York, New York, NY, USA

Elizabeth Zaniewski, Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland

Matthias Egger, Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland

Kara Wools-Kaloustian, School of Medicine, Indiana University, Indianapolis, IN, USA

Constantin T. Yiannoutsos, Department of Biostatistics, R.M. Fairbanks School of Public Health, Indiana University, Indianapolis, IN, USA

Antoine Jaquet, University of Bordeaux, Inserm, French National Research Institute for Sustainable Development (IRD), UMR 1219, Bordeaux, France

Keri N. Althoff, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Jennifer S. Lee, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Yanink Caro-Vega, Departamento de Infectología, Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", Mexico City, Mexico

Paula M. Luz, Instituto Nacional de Infectologia Evandro Chagas, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil

Junko Tanuma, AIDS Clinical Center, National Center for Global Health and Medicine, Tokyo, Japan

Théodore Niyongabo, Centre National de Référence en Matière de VIH/SIDA (CNR), Bujumbura, Burundi

Denis Nash, Institute for Implementation Science in Population Health (ISPH), Graduate School of Public Health and Health Policy, City University of New York, New York, NY, USA

International epidemiology Databases to Evaluate AIDS (IeDEA) consortium

CORRESPONDING AUTHOR: Ellen Brazier, Institute for Implementation Science in Population Health (ISPH), Graduate School of Public Health and Health Policy, City University of New York, 55 West 125th Street, 6th Floor, New York, NY 10027, USA. Email: ellen.brazier@sph.cuny.edu

MAIN POINT: Adoption of Treat-All policies led to decreases in pre-ART CD4 testing among adult ART initiators in L/LMICs, with no immediate increase in VL monitoring after ART initiation, raising concerns about appropriate care of individuals with advanced HIV disease.

© The Author(s) 2021. Published by Oxford University Press for the Infectious Diseases Society of America.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

ABSTRACT

Background: The World Health Organization's Treat-All guidance recommends CD4 testing prior to antiretroviral treatment (ART) initiation, and routine viral load (VL) monitoring (over CD4 monitoring) for patients on ART.

Methods: We used regression discontinuity analyses to estimate changes in CD4 testing and VL monitoring among 547,837 ART-naïve patients enrolling in HIV care during 2006-2018 at 225 clinics in 26 countries where Treat-All policies were adopted. We examined CD4 testing within 12 months before and VL monitoring 6 months after ART initiation among adults (≥ 20 years), adolescents (10-19 years) and children (0-9 years) in low/lower-middle income countries (L/LMICs) and high/upper-middle income countries (H/UMICs).

Results: Treat-All adoption led to an immediate decrease in pre-ART CD4 testing among adults in L/LMICs, from 57.0% to 48.1% (-8.9 percentage points [pp]; 95% CI: -11.0, -6.8), and a small increase in in H/UMICs, from 90.1 to 91.7% (+1.6pp; 95% CI: 0.2, 3.0), with no changes among adolescents or children; decreases in pre-ART CD4 testing accelerated after Treat-All adoption in L/LMICs. In L/LMICs, VL monitoring after ART initiation was low among all patients just before Treat-All; while there was no immediate change at Treat-All adoption, VL monitoring trends significantly increased afterwards. In H/UMICs, VL monitoring increased among adults immediately after Treat-All adoption, from 58.2% to 61.1% (+2.9pp; 95% CI: 0.5, 5.4), with no significant changes among adolescents/children.

Conclusions: While on-ART VL monitoring has improved in L/LMICs, Treat-All adoption has accelerated and disparately worsened suboptimal pre-ART CD4 monitoring, which may compromise care outcomes for individuals with advanced HIV.

KEY WORDS: HIV care, Pre-ART CD4 testing, Viral load monitoring, Treat-All

INTRODUCTION

Country-level adoption of the World Health Organization's 2015 recommendation for universal treatment of all people living with HIV (PLWH) [1]—also known as “Treat-All”—has improved access to life-saving antiretroviral therapy (ART), particularly in low-resource settings where ascertaining treatment eligibility based on CD4 levels constituted a barrier to timely treatment initiation [2, 3]. Nevertheless, pre-ART CD4 testing remains essential for assessing patients' risk of opportunistic infections (OIs) and identifying patients with advanced HIV disease and elevated mortality risks who should be prioritized for differentiated care [4, 5]. Pre-ART CD4 levels also provide important information for monitoring progress towards population health goals of earlier diagnosis and treatment of HIV [6-8].

Despite its importance for guiding HIV care, since adoption of Treat-All, pre-ART CD4 testing is increasingly deprioritized in favor of scaling up viral load (VL) testing for patients on ART [4, 9, 10]. The U.S. President's Emergency Fund for AIDS Relief (PEPFAR) has reduced support for pre-ART CD4 testing—even in settings where capacity for VL testing remains suboptimal [3, 5, 10, 11]—and studies suggest that pre-ART CD4 testing has decreased markedly in recent years [12, 13], raising concerns about potential negative consequences for patient care. While VL monitoring is recommended at 6 and 12 months after ART initiation and at least annually thereafter to ascertain treatment success or failure and to guide decisions regarding regimen switches and differentiated care strategies [14-17], it is not a substitute for pre-ART CD4 testing and it has limited value for assessing disease progression and mortality risks for patients entering or re-engaging in care [18].

The impact of national adoption of Treat-All policies on routine laboratory monitoring practices in HIV care is unknown. Using data from the International epidemiology Databases to Evaluate AIDS (IeDEA) research consortium, we estimated the effect of Treat-All policy adoption on pre-ART CD4 testing practices and on VL monitoring after ART initiation.

I. METHODS

Data sources and management

The IeDEA consortium pools observational clinical data on approximately 1.7 million PLWH ever enrolling in care at approximately 400 care and treatment sites in 46 countries [19]—sites whose practices reflect national and local treatment guidelines. De-identified data were approved for use by local research ethics committees and were standardized in accordance with IeDEA data definitions [20].

Exposure and outcomes

The exposure of interest was enrollment in HIV care before versus on or after national adoption of the World Health Organization's (WHO) Treat-All recommendations. We identified the date when universal ART eligibility was extended to all adult patients in each country, based on policy documents, literature, and inputs from in-country experts, as described elsewhere [12, 21, 22].

Primary outcomes of interest were (1) pre-ART CD4 testing and (2) VL monitoring 6 months after ART initiation among patients with sufficient potential follow-up time (see Inclusion criteria). To align with WHO recommendations that pre-treatment CD4 testing be performed every 6-12 months when ART initiation is delayed [23], we defined pre-ART CD4 testing as the presence of any CD4 measurement (count or percent) within the 12 months prior to and up to 7 days after ART initiation. We defined VL monitoring as the presence of any VL test at 6 months (+/- 3 months) after ART initiation.

Inclusion and exclusion criteria

Patients: All ART-naïve patients who enrolled in HIV care between 2006 and 2018, had complete information on age and sex, and sufficient potential follow-up time between ART initiation and the earliest of database closure, documented transfer to another site, or death were eligible, regardless of age. Analyses of pre-ART CD4 testing and VL monitoring, respectively, were restricted to patients with ≥ 7 days' and ≥ 9 months' potential follow-up time after ART initiation.

Sites: All IeDEA sites that contributed patient data for at least 365 days prior to and after national adoption of Treat-All were eligible. Sites were excluded if enrollment and service delivery dates had been shifted for anonymization purposes.

Countries: Countries where WHO's Treat-All policy was not officially adopted in national guidelines by December 2018 were excluded.

Other definitions

Age group: Adults were defined as ≥ 20 years at enrollment at an IeDEA site, with adolescents defined as 10-19 years, and children defined as < 10 years.

Country income classification: Information on each country's income group in 2017—low- and lower-middle income (L/LMIC) versus high/upper-middle income (H/UMIC)—was compiled from World Bank databases [24].

Statistical analysis

We used descriptive statistics to summarize patient characteristics and the proportion of patients with laboratory monitoring outcomes of interest.

To estimate the effect of national Treat-All policy adoption on laboratory monitoring, we used a sharp regression discontinuity (RD) in time design [25]. For all outcomes, we treated patients' date of enrollment in HIV care as a continuous treatment assignment variable, using the date of national Treat-All policy adoption as a cut-off threshold. Patients enrolling in care prior to the cut-off were considered unexposed to Treat-All, and those enrolling on or after the cut-off were considered exposed.

To assess key RD assumptions, we plotted the density of patients enrolling in HIV care, by month, and examined whether there was evidence of bunching of observations before or after national policy adoption, which would suggest manipulation of enrollment dates. We also used RD analysis to assess systematic differences in patient age and sex distributions before and after Treat-All adoption.

We examined the effect of Treat-All adoption on laboratory testing outcomes for each of the three age groups, stratified by country income level. We used local linear regression models [26] within data-driven Imbens-Kalyanaraman (IK) bandwidth intervals, derived using a rectangular (uniform) kernel [27], to estimate risk differences just before and just after Treat All adoption as:

$$E[Y_i|Z_i] = \beta_0 + \beta_1 Z_i + \beta_2 \times 1[Z_i \geq 0] + \beta_3 Z_i \times 1[Z_i \geq 0] \quad [28]$$

where Y_i is the patient's probability of receiving the laboratory test, Z_i is the number of days between patients' enrollment date and national Treat-All adoption date (negative for patients enrolling before Treat-All adoption), and $1[Z_i \geq 0]$ indicates enrollment on or after the date of Treat-All adoption. Calculated using the subset of observations within IK bandwidth intervals, the effect of interest is the difference in local linear predictions at the threshold (i.e., as the threshold is approached from above versus below) [28].

In sensitivity analyses, we estimated risk differences at the threshold using the IK bandwidths ± 3 months, as well as IK bandwidths computed with a triangular kernel and with a second-order polynomial term. We also estimated differences at the threshold controlling for unbalanced covariates among those enrolling before and after Treat-All adoption. To assess how the local average treatment effect varied with marginal changes in the date of Treat-All adoption, as might occur with heterogeneous site-level policy introduction within countries, we also estimated the treatment effect derivative (TED), which, under the local policy invariance assumption, is equivalent to the marginal threshold treatment effect (MTTE) [29-31]. Finally, for the VL monitoring outcome, we performed an additional sensitivity analysis that excluded patients enrolling in HIV care during the 9 months immediately prior to Treat-All adoption, as VL testing for these patients may have taken place after Treat-All introduction.

To examine trends in the percentage of patients with laboratory monitoring before and after Treat-All adoption, we compared slopes from linear models regressing testing against time for the two years before and after Treat-All adoption, using an interaction term to assess differences in percentage point changes per year (pp/yr) in testing in the pre- and post-Treat-All periods.

All statistical analyses were performed using STATA 15.1 (StataCorp, College Station, TX, USA).

II. RESULTS

Sample characteristics

Data were available for 547,837 patients with ≥ 7 days of potential follow-up time after ART initiation who had enrolled in HIV care at 225 clinics/programs in 26 countries where WHO's Treat-All recommendation had been adopted. Of these, 492,980 patients had sufficient potential follow-up time for assessment of VL monitoring at 6 months after ART initiation.

Most patients were female (62.9%), with a median age at enrollment of 33.7 years (interquartile range 26.7-41.7). The majority of patients were from IeDEA cohorts in East and Southern Africa, and more than 80% had enrolled in care prior to Treat-All adoption (Table 1).

Patients enrolling before and after national Treat-All adoption were similar with respect to age and sex (Table S1A-B), and no major discontinuities were observed in the numbers of patients enrolling in HIV care around the Treat-All threshold date for either analytic sample (Figure S1).

Pre-ART CD4 testing

Among those enrolling in HIV care from 2006 and 2018 and initiating ART, the percentage with a pre-ART CD4 test was 67.1%, 58.1%, and 59.5% for adult, adolescent and pediatric patients, respectively, in L/LMICs and 89.4%, 83.8% and 71.0%, respectively, in H/UMICs (Table 2A-B). In L/LMICs, the percentage of patients with pre-ART CD4 testing was markedly lower after Treat-All adoption, with smaller changes in H/UMICs.

Effect of Treat-All on pre-ART CD4 testing (RD analysis)

In L/LMICs, there was a substantial decrease in pre-ART CD4 testing after Treat-All adoption, with an 8.9 percentage point (pp) decrease (95% CI: -11.0, -6.8) among adults, from 57.0% of patients enrolling in care just before Treat-All adoption to 48.1% just afterwards (Table 2A and Figure 1[A]). Statistically non-significant decreases were observed among adolescents and children. In H/UMICs, where pre-ART CD4 testing was almost universal (90.1%) among adults just before Treat-All adoption, there was a small increase just afterwards (+1.6; 95% CI: +0.2, +3.0), with no changes among adolescents or children (Table 2B). TED estimates were near zero, and RD estimates were robust to alternative bandwidths (Table S2).

Trends in pre-ART CD4 testing before and after Treat-All (slope comparison)

During the two years before Treat-All adoption, pre-ART CD4 testing began decreasing among adult patients in L/LMICs (-2.1pp/yr; 95% CI: -2.9, -1.4), and the decrease accelerated markedly in the two years afterwards (-13.9 pp/yr; 95% CI: -14.7, -13.1) (Table 2A). Similar decreases in the average annual rate of pre-ART CD4 testing were observed in

L/LMICs among adolescents in the two years after Treat-All adoption (-9.3pp/yr; 95% CI: -12.5, -6.0) and among children (-12.2pp/yr (95% CI: -15.8, -8.7).

In H/UMICs, the rate of pre-ART CD4 testing was stable among all patients during the two years before Treat-All adoption, and it decreased among adults (-6.6pp/yr; 95% CI: -7.2, -5.9) and adolescents (-5.7 pp/yr; 95% CI: -9.1, -2.3) during the two years after Treat-All adoption, with no change among children (Table 2B).

VL monitoring after ART initiation

Overall, 10.6-11.9% of patients enrolling in HIV care from 2006 to 2018 in L/LMICs had a VL test at 6 months after ART initiation, versus 49.3-55.8% of patients in H/UMICs (Table 3A-B).

Effect of Treat-All on VL monitoring (RD analysis)

There were statistically non-significant decreases in VL monitoring among adults, adolescents and children in L/LMICs after Treat-All adoption (Table 3A). In contrast, in H/UMICs, a small but significant increase in VL monitoring was observed among adults (+2.9pp; 95% CI: 0.5, 5.4), from 58.2% of patients enrolling in care just before Treat-All adoption to 61.1% just afterwards (Table 3B). No significant changes were observed among adolescents or children.

TED estimates were close to zero or non-significant. In H/UMICs, sensitivity analyses generated qualitatively consistent results (Table S3B). In L/LMICs, sensitivity analyses estimated with bandwidths larger than the IK bandwidths showed statistically significant

decreases in VL monitoring among adults, adolescents and children after Treat-All adoption. Sensitivity analyses that excluded patients enrolling in the 9 months before Treat-All adoption also showed a significant decrease in VL monitoring among children in L/LMICs (-7.4pp; 95% CI: -13.1, -1.8), with no change among adults or adolescents (Table S3A and Figure S2).

VL monitoring trends before and after Treat-All (slope comparison)

While RD results showed no changes in VL monitoring after Treat-All adoption in L/LMICs, rates of VL monitoring, which began increasing prior to Treat-All, continued to increase among all age groups during the two years after Treat-All adoption, and the average annual rate of increase was significantly and markedly higher than during the two years prior (Table 3A and Figure 1[B]). In contrast, in H/UMICs where levels were already high, the average annual rate of VL monitoring among adults decreased slightly in the two years after Treat-All adoption—a change from pre-Treat-All trends (Table 3B). Among adolescents in H/UMICs, the rate of VL monitoring stopped increasing after Treat-All adoption, and there was no significant change in the rate of VL monitoring among adolescents and children in H/UMICs.

DISCUSSION

National adoption of Treat-All policies has been followed by substantial decreases in pre-ART CD4 testing among adults in L/LMICs, whereas there were small but significant increases in pre-ART CD4 testing among adults in H/UMICs. While the elimination of CD4 count-based eligibility requirements has improved access to life-saving HIV treatment in L/LMICs, decreases in pre-ART CD4 testing may be an unintended consequence of Treat-All

adoption. These decreases may have substantial clinical importance in settings where many patients enroll in HIV care with advanced disease [32] and are at risk of early mortality prior to and immediately after ART initiation [4]. Without pre-ART CD4 testing, many who would benefit from differentiated care for advanced HIV, as well as screening, prophylaxis and treatment for OIs are unlikely to be identified [4]. Although other studies have found no evidence that Treat-All adoption “crowds out” sicker patients [12, 33], the elimination of CD4 testing for ascertaining treatment eligibility may have led to declines in the quality of care for some HIV patients under Treat-All.

No changes in pre-ART CD4 testing were observed among children—results that are in line with expectations, as pediatric Treat-All policies were recommended by the WHO and incorporated into national treatment guidelines before ART eligibility expansions for older age groups [34]. Nonetheless, low rates of pre-ART CD4 testing in children in L/LMICs are concerning, as late diagnosis of HIV among children remains prevalent in low-resource settings because of gaps in capacity for early infant diagnosis and rapid disease progression among children [35-38]. Children living with HIV, particularly those entering care with advanced HIV, also have persistently high mortality rates [37, 39].

It could be theorized that decreases in pre-ART CD4 testing in L/LMICs reflect the reallocation of resources toward VL monitoring, which has long been recommended over CD4 testing for identifying treatment failure [17]. Although rates of VL monitoring were increasing among all age groups in L/LMICs in the two years before Treat-All adoption, and the rate of change increased afterwards, with marked improvements by two years after Treat-All adoption, the lack of any immediate increases in VL monitoring in L/LMICs at Treat-All adoption likely reflects the limited capacity for viral load monitoring in these settings at the

time of Treat-All adoption, as well as delays in adopting WHO guidance on VL monitoring [40].

Importantly, our analysis highlights stark disparities in HIV-related laboratory monitoring by country income level that have been exacerbated by Treat-All policies. For pre-ART CD4 testing, these disparities appear to have widened just after Treat-All adoption, with adult patients in H/UMICs more than twice as likely as those in L/LMICs to have pre-ART CD4 testing and VL monitoring after ART initiation. These disparities were even larger among adolescents and children. Disparities in pre-ART CD4 testing have continued to widen after Treat-All adoption. Although disparities in VL monitoring appear to be lessened since Treat-All adoption, two years after Treat-All adoption, fewer than half of all patients in L/LMICs had a VL test 6 months after initiating ART.

The use of a sharp RD design and real-world service delivery data across more than 200 HIV clinics in high- and low-resource settings are important strengths of this analysis. Analogous to a randomized controlled trial with perfect compliance when certain assumptions are met [28], this design provides support for interpreting differences in laboratory monitoring at the Treat-All threshold as causal effects. Important limitations should also be noted. First, limited data on patient characteristics restricted our ability to comprehensively assess differences between those enrolling in HIV care before and after Treat-All adoption. Where differences in the age and sex distributions of patients were observed, they were small in magnitude and did not influence effect estimates. Secondly, lags in clinic-level introduction of Treat-All policies relative to national policy adoption are known to have varied across clinics and countries included in this analysis, particularly in high-resource settings [22]. Small and non-significant changes in laboratory monitoring may reflect the heterogeneous timing of Treat-

All policy introduction at clinics in these settings. In L/LMICs, where we have previously found minimal lags in clinic-level introduction of national Treat-All policies [22], our near-zero and non-significant TED estimates suggest that marginal differences in the timing of Treat-All introduction at the clinic level would have minimal influence on our effect estimates. Finally, pooling data from diverse clinics and settings within broad country income-group classifications likely masks substantial heterogeneity between ART programs and countries. Accordingly, further research to examine the impact of Treat-All adoption on laboratory testing practices at regional and national levels and by level of the health system is warranted, along with research on prophylactic treatment of OIs in settings where pre-ART CD4 testing is not performed.

III. CONCLUSION

While the WHO's Treat-All recommendation has increased access to life-saving treatment, it significantly reduced pre-ART CD4 testing among adult patients in L/LMICs, and disparities between high- and low-income settings in laboratory monitoring around ART initiation have widened with the roll-out of Treat-All. This may have exacerbated gaps in the quality of HIV care and related disparities. Given the importance of pre-ART CD4 testing for the identification of individuals who would benefit from an enhanced treatment package, including prophylaxis against OIs, and for efforts to track progress related to population-level goals of earlier diagnosis and treatment initiation, donors and governments should identify and address barriers to pre-ART CD4 testing while continuing to support the scale-up of VL testing.

NOTES

ACKNOWLEDGEMENTS

The authors acknowledge the patients and staff at all facilities who contributed data to this study, as well as the site investigators and data managers across the IeDEA collaboration (see Supplementary File 2).

FUNDING

This work was supported by the U.S. National Institutes of Health's National Institute of Allergy and Infectious Diseases, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the National Cancer Institute, the National Institute of Mental Health, the National Institute on Drug Abuse, the National Heart, Lung, and Blood Institute, the National Institute on Alcohol Abuse and Alcoholism, the National Institute of Diabetes and Digestive and Kidney Diseases, the Fogarty International Center, and the National Library of Medicine: Asia-Pacific [grant number U01AI069907]; Caribbean, Central and South America network for HIV epidemiology (CCASAnet) [grant number U01AI069923]; Central Africa [grant number U01AI096299]; East Africa [grant number U01AI069911]; NA-ACCORD [grant number U01AI069918]; Southern Africa [grant number U01AI069924]; West Africa [grant number U01AI069919]. This work is solely the responsibility of the authors and does not necessarily represent the official views of any of the institutions mentioned above.

CONFLICTS OF INTEREST

K.N.A. reports grants from NIH during the conduct of this study, as well as personal fees from the All of Us study, Trio Health, and MedIQ, outside the submitted work. K.W-K. reports grants from NIH during the conduct of this study and grants from NIH outside the submitted work. E.B., O.T., and J.S.L. report grants from NIH. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and report no potential conflicts.

Accepted Manuscript

REFERENCES

1. World Health Organization. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva, Switzerland, **2015** September 2015.
2. Moorhouse M, Conradie F, Venter F. What is the role of CD4 count in a large public health antiretroviral programme? *Southern African journal of HIV medicine* **2016**; 17(1): 446-.
3. Peeling RW, Ford N. Reprising the role of CD4 cell count in HIV programmes. *The Lancet HIV* **2017**; 4(9): e377-e8.
4. Ehrenkranz PD, Baptiste SL, Bygrave H, et al. The missed potential of CD4 and viral load testing to improve clinical outcomes for people living with HIV in lower-resource settings. *PLoS Medicine* **2019**; 16(5): e1002820-e.
5. Tenforde MW, Walker AS, Gibb DM, Manabe YC. Rapid antiretroviral therapy initiation in low- and middle-income countries: A resource-based approach. *PLoS Medicine* **2019**; 16(1): e1002723-e.
6. Nash D, Robertson M. How to Evolve the Response to the Global HIV Epidemic With New Metrics and Targets Based on Pre-Treatment CD4 Counts. *Current HIV/AIDS Reports* **2019**; 16(4): 304-13.
7. Ford N, Meintjes G, Vitoria M, Greene G, Chiller T. The evolving role of CD4 cell counts in HIV care. *Current Opinion in HIV and AIDS* **2017**; 12(2): 123-8.
8. Lodi S, Phillips A, Touloumi G, et al. Time From Human Immunodeficiency Virus Seroconversion to Reaching CD4+ Cell Count Thresholds <200, <350, and <500 Cells/mm³: Assessment of Need Following Changes in Treatment Guidelines. *Clinical Infectious Diseases* **2011**; 53(8): 817-25.
9. Clinton Health Access Initiative (CHAI). The state of the HIV market in low- and middle-income countries. Boston, USA, **2019**.

10. U.S. President's Emergency Plan for AIDS Relief (PEPFAR). 2018 Country Operational Plan Guidance for Standard Process Countries. Available at: https://na.usembassy.gov/wp-content/uploads/sites/132/PEPFAR-COP18-Guidance_FINAL-1.pdf. Accessed October 15, 2020.
11. Clinton Health Access Initiative (CHAI). The state of the HIV treatment, testing, and prevention markets in low and middle-income countries, 2017–2022, **2018**.
12. Tymejczyk O, Brazier E, Yiannoutsos CT, et al. Changes in rapid HIV treatment initiation after national "treat all" policy adoption in 6 sub-Saharan African countries: Regression discontinuity analysis. *PLoS Medicine* **2019**; 16(6): e1002822-e.
13. Zaniewski E, Dao Ostinelli CH, Chammartin F, et al. Trends in CD4 and viral load testing 2005 to 2018: multi-cohort study of people living with HIV in Southern Africa. *Journal of the International AIDS Society* **2020**; 23(7): e25546.
14. Lynen L, Van Griensven J, Elliott J. Monitoring for treatment failure in patients on first-line antiretroviral treatment in resource-constrained settings. *Curr Opin HIV AIDS* **2010**; 5(1): 1-5.
15. Sigaloff KC, Hamers RL, Wallis CL, et al. Unnecessary antiretroviral treatment switches and accumulation of HIV resistance mutations; two arguments for viral load monitoring in Africa. *J Acquir Immune Defic Syndr* **2011**; 58(1): 23-31.
16. Phillips A, Shroufi A, Vojnov L, et al. Sustainable HIV treatment in Africa through viral-load-informed differentiated care. *Nature* **2015**; 528(7580): S68-76.
17. World Health Organization (WHO). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization, **2013**.

18. Lawn SD, Harries AD, Anglaret X, Myer L, Wood R. Early mortality among adults accessing antiretroviral treatment programmes in sub-Saharan Africa. *Aids* **2008**; 22(15): 1897-908.
19. IeDEA. International Epidemiologic Databases to Evaluate AIDS. Available at: <https://www.iedea.org/>. Accessed June 1, 2018.
20. Duda SN, Musick BS, Davies M-A, et al. The IeDEA Data Exchange Standard: a common data model for global HIV cohort collaboration. medRxiv **2020**: 2020.07.22.20159921.
21. Tymejczyk O, Brazier E, Yiannoutsos C, et al. HIV treatment eligibility expansion and timely antiretroviral treatment initiation following enrollment in HIV care: A meta-regression analysis of programmatic data from 22 countries. *PLoS Med* **2018**; 15(3): e1002534.
22. Brazier E, Maruri F, Duda SN, et al. Implementation of “Treat-all” at adult HIV care and treatment sites in the Global IeDEA Consortium: results from the Site Assessment Survey. *Journal of the International AIDS Society* **2019**; 22(7): e25331.
23. World Health Organization. Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection. Recommendations for a Public Health Approach. Geneva, Switzerland, **2016**.
24. The World Bank. World Bank list of economies, June 2017. Available at: <https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups>. Accessed Nov 15 2017.
25. Hausman C, Rapson DS. Regression Discontinuity in Time: Considerations for Empirical Applications. *Annual Review of Resource Economics* **2018**; 10(1): 533-52.
26. Hahn J, Todd P, Van der Klaauw W. Identification and Estimation of Treatment Effects with a Regression-Discontinuity Design. *Econometrica* **2001**; 69(1): 201-9.

27. Imbens G, Kalyanaraman K. Optimal Bandwidth Choice for the Regression Discontinuity Estimator. *The Review of Economic Studies* **2012**; 79(3): 933-59.
28. Bor J, Moscoe E, Mutevedzi P, Newell ML, Barnighausen T. Regression discontinuity designs in epidemiology: causal inference without randomized trials. *Epidemiology* **2014**; 25(5): 729-37.
29. Dong Y, Lewbel A. Identifying the Effect of Changing the Policy Threshold in Regression Discontinuity Models. *The Review of Economics and Statistics* **2015**; 97(5): 1081-92.
30. Cerulli G, Dong Y, Lewbel A, Poulsen A. Testing Stability of Regression Discontinuity Models. *Regression Discontinuity Designs Vol. 38: Emerald Publishing Limited*, **2017**:317-39.
31. Wing C, Bello-Gomez RA. Regression Discontinuity and Beyond: Options for Studying External Validity in an Internally Valid Design. *American Journal of Evaluation* **2018**; 39(1): 91-108.
32. The IeDEA and COHERE Cohort Collaborations. Global Trends in CD4 Cell Count at the Start of Antiretroviral Therapy: Collaborative Study of Treatment Programs. *Clinical Infectious Diseases* **2018**; 66(6): 893-903.
33. Tymejczyk O, Brazier E, Yiannoutsos C, et al. HIV treatment eligibility expansion and timely antiretroviral treatment initiation following enrollment in HIV care: A metaregression analysis of programmatic data from 22 countries. *PLoS Medicine* **2018**; 15(3): e1002534.
34. Burrage A, Patel M, Mirkovic K, et al. Trends in Antiretroviral Therapy Eligibility and Coverage Among Children Aged <15 Years with HIV Infection - 20 PEPFAR-Supported Sub-Saharan African Countries, 2012-2016. *MMWR Morb Mortal Wkly Rep* **2018**; 67(19): 552-5.

35. Koller M, Patel K, Chi BH, et al. Immunodeficiency in children starting antiretroviral therapy in low-, middle-, and high-income countries. *Journal of acquired immune deficiency syndromes (1999)* **2015**; 68(1): 62-72.
36. Wools-Kaloustian K, Marete I, Ayaya S, et al. Time to First-Line ART Failure and Time to Second-Line ART Switch in the IeDEA Pediatric Cohort. *JAIDS Journal of Acquired Immune Deficiency Syndromes* **2018**; 78(2): 221-30.
37. Elyanu P. Trends in advanced HIV disease and long-term outcomes of HIV infected children treated with antiretroviral therapy in Eastern and Southern Africa: 2003-2017. Houston: University of Texas, **2019**.
38. The European Pregnancy Paediatric HIV Cohort Collaboration Study Group in EuroCoord (EPPICC). Prevalence and Clinical Outcomes of Poor Immune Response Despite Virologically Suppressive Antiretroviral Therapy Among Children and Adolescents With Human Immunodeficiency Virus in Europe and Thailand: Cohort Study. *Clinical Infectious Diseases* **2019**; 70(3): 404-15.
39. Bekker L-G, Alleyne G, Baral S, et al. Advancing global health and strengthening the HIV response in the era of the Sustainable Development Goals: the International AIDS Society & Lancet Commission. *The Lancet* **2018**; 392(10144): 312-58.
40. Roberts T, Cohn J, Bonner K, Hargreaves S. Scale-up of Routine Viral Load Testing in Resource-Poor Settings: Current and Future Implementation Challenges. *Clin Infect Dis* **2016**; 62(8): 1043-8.

Table 1. Sample characteristics, by study outcome

Characteristics at enrollment in HIV care	Pre-ART CD4 testing*	Viral load monitoring at 6 months after ART initiation**
	N (% of total)	N (% of total)
Patients	547,837	492,980
Sites	225	224
Countries	26	26
Region		
Asia-Pacific	7,483 (1.4%)	7,076 (1.4%)
Central Africa	31,936 (5.8%)	31,598 (6.4%)
East Africa	185,469 (33.9%)	168,495 (34.2%)
North America	25,465 (4.7%)	24,307 (4.9%)
Southern Africa	282,810 (51.6%)	248,607 (50.4%)
West Africa	14,674 (2.7%)	12,897 (2.6%)
Country income level		
Low/lower-middle income	327,750 (59.8%)	292,380 (59.3%)
High/upper-middle income	220,087 (40.2%)	200,600 (40.7%)
Sex		
Male	203,359 (37.1%)	181,545 (36.8%)
Female	344,478 (62.9%)	311,435 (63.2%)
Age at enrollment (Years)		
Median (IQR)	33.7 (26.7 -41.7)	33.7 (26.8 -41.7)
Age group at enrollment		
Adults (>19 years)	494,661 (90.3%)	445,893 (90.5%)
Adolescents (10-19 years)	21,336 (3.9%)	17,992 (3.7%)

Children (< 10 years)	31,840 (5.8%)	29,095 (5.9%)
Period of enrollment		
Before Treat-All introduction	456,466 (83.3%)	424,671 (86.1%)
After Treat-All introduction	91,371 (16.7%)	68,309 (13.9%)

*ART-naïve patients enrolling in HIV care 2006-2018, with at least 7 days of potential follow-up time after

ART initiation

**ART-naïve patients enrolling in HIV care 2006-2018 with at least 9 months (273 days) of potential follow-up time after ART initiation

Accepted Manuscript

Table 2A. Pre-ART CD4 testing (within 12 months before ART initiation), before and after Treat-All introduction in low and lower-middle income countries

Patient group	Adults (>19 yrs) [‡]	Adolescents (10-19 yrs) [§]	Children (<10 yrs) [◊]
N	291,428	14,363	21,959
Baseline CD4 monitoring	195,642 (67.1%)	8,338 (58.1%)	13,070 (59.5%)
Before Treat-All adoption	181,835 (73.4%)	7,665 (64.8%)	12,691 (62.9%)
After Treat-All adoption	13,807 (31.6%)	673 (26.6%)	379 (21.3%)
Risk difference at the Treat-All adoption threshold (95% CI)*	-8.9 (95% CI: -11.0, -6.8)	-6.0 (95% CI: -12.4, 0.4)	-3.6 (95% CI: -8.7, 1.4)
p-value	<.0001	0.067	0.158
Imbens-Kalyanaraman bandwidth (days)	282	448	756
N within bandwidth	34,509	3,421	4,642
Treatment Effect Derivative (TED) (95% CI)	-0.073 (-0.086, -0.060)	-0.013 (-0.039, 0.012)	-0.03 (-0.042, -0.018)
TED p-value	<.0001	0.300	<.0001
Predicted outcomes at the Treat-All threshold*			
Enrollment just before Treat-All adoption	57.0% (55.5%, 58.4%)	41% (36.3%, 45.7%)	34.5% (31%, 38.0%)
Enrollment just after Treat-All adoption	48.1% (46.6%, 49.5%)	35% (30.7%, 39.4%)	30.8% (27.2%, 34.5%)
Relative change at threshold	-15.6%	-14.6%	-10.6%
Slopes before and after Treat-All adoption**			

Patient group	Adults (>19 yrs) [‡]	Adolescents (10-19 yrs) [§]	Children (<10 yrs) [◇]
N	291,428	14,363	21,959
Percentage point change before Treat-All	-2.1 (-2.9, -1.4)	-4.4 (-7.4, -1.4)	0.3 (-2.5, 3.1)
Percentage point change after Treat-All	-13.9 (-14.7, -13.1)	-9.3 (-12.5, -6.0)	-12.2 (-15.8, -8.7)
P-value for interaction term (difference in slopes)	<.0001	0.037	<.0001

CI: Confidence interval

*Risk difference and predicted outcomes at the Treat-All threshold are from regression discontinuity analysis estimating the difference in local linear predictions at the threshold (i.e., in the limit, as the threshold is approached from above and below). The Imbens-Kalyanaraman bandwidth defines the region in which the relationship between enrollment timing and testing outcome is assumed to be linear in local linear regression models.

**Slope comparison is from separate linear regression models comparing the two years before Treat-All adoption and after adoption.

[‡]Burundi, Cambodia, Cameroon, Cote d'Ivoire, Kenya, Lesotho, Malawi, Mozambique, Republic of Congo, Rwanda, Senegal, Tanzania, Uganda, Zimbabwe.

[§]Benin, Burundi, Cambodia, Cameroon, Cote d'Ivoire, Ghana, India, Kenya, Lesotho, Malawi, Mozambique, Republic of Congo, Rwanda, Senegal, Tanzania, Uganda, Vietnam, Zimbabwe.

[◇]Benin, Burundi, Cambodia, Cameroon, Cote d'Ivoire, Ghana, India, Kenya, Lesotho, Malawi, Mozambique, Republic of Congo, Rwanda, Tanzania, Uganda, Vietnam, Zimbabwe

Table 2B. Pre-ART CD4 testing (within 12 months before ART initiation), before and after Treat-All introduction in high and upper-middle income countries

Patient group	Adults (>19 yrs) ^{**}	Adolescents (10-19 yrs) ^{**}	Children (<10 yrs) [∞]
N	203,233	6,973	9,881
Baseline CD4 monitoring	181,643 (89.4%)	5,844 (83.8%)	7,014 (71.0%)
Before Treat-All adoption	146,590 (90.3%)	4,490 (84.4%)	6,497 (71.8%)
After Treat-All adoption	35,053 (85.8%)	1,354 (82%)	517 (62.4%)
Risk difference at the Treat-All adoption threshold (95% CI)*	1.6 (95% CI: 0.2, 3.0)	-0.5 (95% CI: -5.6, 4.7)	3.1 (95% CI: -5.4, 11.6)
p-value	0.022	0.854	0.477
Imbens-Kalyanaraman bandwidth (days)	289	739	761
N within bandwidth	27,283	2,797	1,922
Treatment Effect Derivative (TED) (95% CI)	-0.013 (-0.022, -0.005)	-0.024 (-0.037, -0.011)	0 (-0.021, 0.020)
TED p-value	0.002	<.0001	0.985
Predicted outcomes at the Treat-All threshold*			
Enrollment just before Treat-All adoption	90.1% (89.1%, 91.1%)	88.9% (85.2%, 92.6%)	62.7% (57%, 68.4%)
Enrollment just after Treat-All adoption	91.7% (90.8%, 92.6%)	88.4% (84.8%, 92.0%)	65.8% (59.5%, 72.1%)
Relative change at threshold	1.8%	-0.5%	4.9%
Slopes before and after Treat-All adoption**			
Percentage point change before Treat-All	0.2 (-0.3, 0.8)	3.4 (0, 6.8)	-3.2 (-8.2, 1.7)

Patient group	Adults (>19 yrs) ^{‡‡}	Adolescents (10-19 yrs) ^{§§}	Children (<10 yrs) [∞]
N	203,233	6,973	9,881
Percentage point change after Treat-All	-6.6 (-7.2, -5.9)	-5.7 (-9.1, -2.3)	-3.8 (-10.0, 2.3)
P-value for interaction term (difference in slopes)	<.0001	<.0001	0.880

CI: Confidence interval

*Risk difference and predicted outcomes at the Treat-All threshold are from regression discontinuity analysis estimating the difference in local linear predictions at the threshold (i.e., in the limit, as the threshold is approached from above and below). The Imbens-Kalyanaraman bandwidth defines the region in which the relationship between enrollment timing and testing outcome is assumed to be linear in local linear regression models.

**Slope comparison is from separate linear regression models comparing the two years before Treat-All adoption and after adoption.

‡‡ Canada, China including Hong Kong SAR, South Africa, South Korea, United States.

§§ Canada, Malaysia, South Africa, South Korea, Thailand, United States.

∞ Malaysia, South Africa, Thailand.

Table 3A. Viral load monitoring after ART initiation, before and after Treat-All introduction in low/lower-middle income countries

Patient group	Adults (>19 yrs)[‡]	Adolescents (10-19 yrs)[§]	Children (<10 yrs)[◇]
N	260,735	11,619	20,026
Viral load monitoring after ART initiation	31,147 (11.9%)	1,295 (11.1%)	2,128 (10.6%)
Before Treat-All adoption	20,930 (9.1%)	938 (9.1%)	1,858 (9.9%)
After Treat-All adoption	10,217 (34.7%)	357 (26.5%)	270 (22.6%)
Risk difference at the Treat-All adoption threshold (95% CI)*	-1.7 (95% CI: -3.5, 0.2)	-6.0 (95% CI: -12.5, 0.5)	-4.7 (95% CI: -10.6, 1.1)
p-value	0.074	0.069	0.112
Imbens-Kalyanaraman bandwidth, days	328	421	423
N within bandwidth	37,204	2,431	2,463
Treatment Effect Derivative (TED) (95% CI)	-0.007 (-0.017, 0.003)	-0.01 (-0.039, 0.018)	0.018 (-0.008, 0.045)
TED p-value	0.174	0.485	0.171
Predicted outcomes at the Treat-All threshold*			
Enrollment just before Treat-All adoption	30.1% (28.8%, 31.4%)	24.8% (20.4%, 29.2%)	19.8% (15.7%, 23.9%)
Enrollment just after Treat-All adoption	28.5% (27.2%, 29.7%)	18.8% (14.0%, 23.5%)	15.1% (10.9%, 19.2%)
Relative change at threshold	-5.5%	-24.3%	-23.9%
Slopes before and after Treat-All adoption**			

Patient group	Adults (>19 yrs) [‡]	Adolescents (10-19 yrs) [§]	Children (<10 yrs) [◇]
N	260,735	11,619	20,026
Percentage point change before Treat-All	7.2 (6.4, 7.9)	5.0 (2.3, 7.8)	2.9 (0.4, 5.5)
Percentage point change after Treat-All	14.3 (13.2, 15.4)	15.7 (10.8, 20.6)	23.4 (17.9, 28.8)
P-value for interaction term (difference in slopes)	<.0001	<.0001	<.0001

CI: Confidence interval

*Risk difference and predicted outcomes at the Treat-All threshold are from regression discontinuity analysis estimating the difference in local linear predictions at the threshold (i.e., in the limit, as the threshold is approached from above and below). The Imbens-Kalyanaraman bandwidth defines the region in which the relationship between enrollment timing and testing outcome is assumed to be linear in local linear regression models.

**Slope comparison is from separate linear regression models comparing the two years before Treat-All adoption and after adoption.

[‡] Burundi, Cambodia, Cameroon, Cote d'Ivoire, Kenya, Lesotho, Malawi, Mozambique, Republic of Congo, Rwanda, Senegal, Tanzania, Uganda, Zimbabwe

[§] Benin, Burundi, Cambodia, Cameroon, Cote d'Ivoire, Ghana, India, Kenya, Lesotho, Mozambique, Republic of Congo, Rwanda, Senegal, Tanzania, Uganda, Vietnam, Zimbabwe

[◇] Benin, Burundi, Cambodia, Cameroon, Cote d'Ivoire, Ghana, India, Kenya, Lesotho, Malawi, Mozambique, Republic of Congo, Rwanda, Tanzania, Uganda, Vietnam, Zimbabwe

Table 3B. Viral load monitoring after ART initiation, before and after Treat-All introduction in high/upper-middle income countries

Patient group	Adults (>19 yrs)^{‡‡}	Adolescents (10-19 yrs)^{§§}	Children (<10 yrs)^{ⒹⒹ}
N	185,158	6,373	9,069
Viral load monitoring after ART initiation	103,273 (55.8%)	3,144 (49.3%)	4,773 (52.6%)
Before Treat-All adoption	83,411 (55.2%)	2,447 (49.3%)	4,391 (52.6%)
After Treat-All adoption	19,862 (58.1%)	697 (49.5%)	382 (52.8%)
Risk difference at the Treat-All adoption threshold (95% CI)*	2.9 (95% CI: 0.5, 5.4)	-5.0 (95% CI: -13.5, 3.4)	7.7 (95% CI: -3.7, 19.2)
p-value	0.020	0.241	0.186
Imbens-Kalyanaraman bandwidth, days	275	596	472
N within bandwidth	23,939	2,141	1,172
Treatment Effect Derivative (TED) (95% CI)	-0.018 (-0.034, -0.002)	-0.019 (-0.044, 0.005)	-0.014 (-0.057, 0.028)
TED p-value	0.026	0.123	0.515
Predicted outcomes at the Treat-All threshold*			
Enrollment just before Treat-All adoption	58.2% (56.4%, 60.0%)	54.6% (48.4%, 60.8%)	50.7% (42.6%, 58.9%)
Enrollment just after Treat-All adoption	61.1% (59.5%, 62.8%)	49.6% (43.9%, 55.3%)	58.5% (50.4%, 66.5%)
Relative change at threshold	5.0%	-9.2%	15.2%
Slopes before and after Treat-All adoption**			
Percentage point change before Treat-			
All	3.4 (2.4, 4.3)	6.3 (1.4, 11.2)	-3.7 (-9.1, 1.7)
Percentage point change after Treat-All	-4.2 (-5.2, -3.2)	-3.0 (-8.1, 2.0)	-4.7 (-11.7, 2.4)

Patient group	Adults (>19 yrs) ^{‡‡}	Adolescents (10-19 yrs) ^{§§}	Children (<10 yrs) ^{∅∅}
N	185,158	6,373	9,069
P-value for interaction term (difference in slopes)	<.0001	0.009	0.834

CI: Confidence interval

*Risk difference and predicted outcomes at the Treat-All threshold are from regression discontinuity analysis estimating the difference in local linear predictions at the threshold (i.e., in the limit, as the threshold is approached from above and below). The Imbens-Kalyanaraman bandwidth defines the region in which the relationship between enrollment timing and testing outcome is assumed to be linear in local linear regression models.

**Slope comparison is from separate linear regression models comparing the two years before Treat-All adoption and after adoption.

‡‡ Canada, China including Hong Kong SAR, South Africa, South Korea, United States

§§ Canada, Malaysia, South Africa, South Korea, Thailand, United States

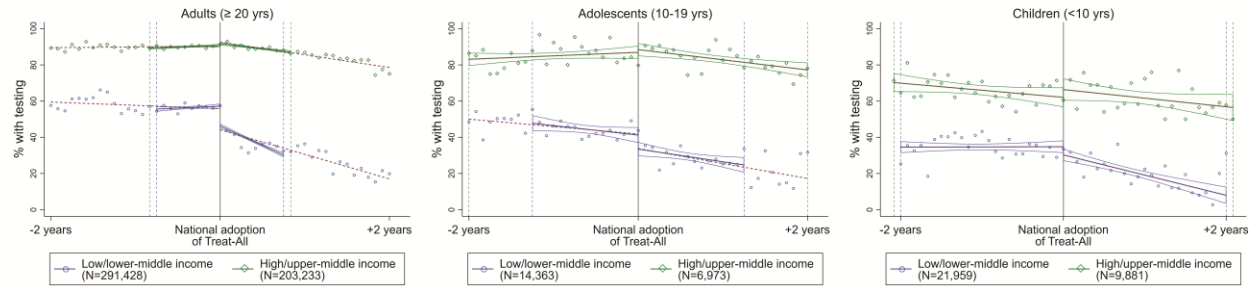
∅∅ Malaysia, South Africa, Thailand

Figure 1: Trends in pre-ART CD4 testing and viral load monitoring before and after Treat-All adoption, by age group and country income level

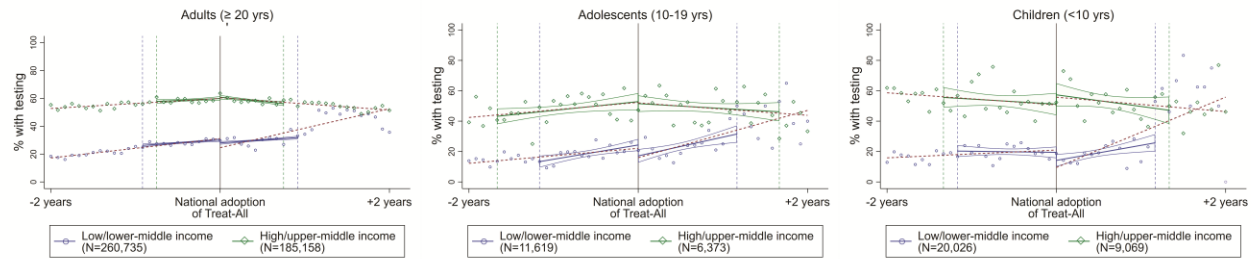
Accepted Manuscript

Figure 1

A. PRE-ART CD4 TESTING



B. VIRAL LOAD MONITORING AT 6 MONTHS AFTER ART INITIATION



Solid blue/green lines: Predicted rate of testing within IK bandwidth before and after Treat-All adoption
 Dotted red lines: Predicted rate of testing in the two years before and after Treat-All adoption
 Dotted blue/green vertical lines: IK bandwidths

Acc